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Anticancer Treatments and Female Fertility: Clinical Concerns and Role of Oncologists in Oncofertility Practice

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Abstract

Introduction: Anticancer treatments such as aggressive chemotherapy and radiotherapy have deleterious gonadotoxic side effects and are considered the most common causes of pathological and iatrogenic fertility loss in women.

Areas Covered: In order to preserve fertility of young women and girls with cancer, several established, experimental, and debatable options can be offered in the emerging field of oncofertility. This article reviews the effects of anticancer treatments on female fertility and discusses the current challenges and future directions of fertility preservation options that can be offered to the female patients with cancer.

Expert Commentary: Although promising, several medical, economic, social and legal barriers face oncofertility practice around the globe especially in underserved areas. To overcome such barriers, more effective solutions should be provided to spread awareness and enhance communication between patients, oncologists and gynecologists. Early referral by oncologists before initiation of chemotherapy and radiotherapy is an important key factor for success in female fertility preservation strategies.

Keywords

Anticancer Treatments; Gonadotoxicity; Female Fertility Preservation; Oncofertility; Female Fertility Loss

1. Introduction

Fertility loss is not rare in women. This condition results from complete depletion of ovarian follicles and oocytes that therefore leads to permanent inability of a woman to conceive. Female fertility loss can be either physiological due to menopause or pathological due to gonadotoxicity, premature ovarian failure (POF) before the age 40, bilateral oophorectomy, gonadal agenesis and other genetic disorders [1, 2, 3].

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Anticancer treatments such as aggressive chemotherapy and radiotherapy have deleterious gonadotoxic side effects and are considered the most common causes of pathological and iatrogenic fertility loss in women [4, 5, 6, 7]. Each year worldwide, over 6.6 million women are diagnosed with cancer [8], and about 10% of them are diagnosed during their reproductive age (age < 40) [9, 10]; they usually receive aggressive chemotherapy and radiotherapy that may cause gonadotoxicity, POF and subsequent fertility loss in more than 80% of cases [11, 12].

2. Anticancer Treatments and Female Fertility

2.1. Anticancer treatments-induced gonadotoxicity

In young women (age < 40) and girls with cancer, gonadotoxicity usually occurs when ovaries are exposed to alkylating chemotherapy such as cyclophosphamide, ifosfamide, busulfan, or ionizing radiotherapy to pelvis and abdomen or cranial and total body irradiation (TBI). Nevertheless, the following anticancer treatments have lower risks for gonadotoxicity depending on the dose, dosage and the age of the patient: doxorubicin, epirubicin, cisplatin, carboplatin, methotrexate, fluorouracil, vincristine, bleomycin, dactinomycin and radiotherapy excluding pelvis, abdomen and head. As guidelines, some important reports published by American Society of Clinical Oncology (ASCO) classified anticancer treatments according to their risk of gonadotoxicity in women (Table 1) [13, 14].

Anticancer treatments with high risk (> 80%) of gonadotoxicity include: (1) Hematopoietic stem cell transplantation (HSCT) with cyclophosphamide/total body irradiation (TBI) or cyclophosphamide/busulfan, (2) External beam radiation to a field that includes the ovaries, (3) CMF, CEF, CAF X 6 cycles in women age 40 and older (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, epirubicin) [13, 14].

Anticancer treatments with intermediate risk (20–80%) of gonadotoxicity include: (1) CMF, CEF, CAF X 6 cycles in women age 30–39 (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, epirubicin), (2) AC X 4 cycles in women age 40 and older (adjuvant breast cancer therapy with doxorubicin/cyclophosphamide) [13, 14].

Anticancer treatments with lower risk (< 20%) of gonadotoxicity include: (1) ABVD (doxorubicin/bleomycin/vinblastine/dacarbazine), (2) CHOP X 4–6 cycles (cyclophosphamide/doxorubicin/vincristine/prednisone), (3) CVP (cyclophosphamide/vincristine/prednisone), (4) Acute myeloid leukemia (AML) therapy (anthracycline/cytarabine), (5) Acute lymphoblastic leukemia (ALL) therapy (multi-agent), (6) CMF, CEF, CAF X 6 cycles in women less than 30 (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, epirubicin), (7) AC X 4 cycles in women less than 40 (adjuvant breast cancer therapy with doxorubicin/cyclophosphamide) [13, 14]

Anticancer treatments with very low or no risk of gonadotoxicity include methotrexate, fluorouracil, vincristine, bleomycin, and dactinomycin. Anticancer treatments with unknown

risk of gonadotoxicity include taxanes, oxaliplatin, irinotecan, monoclonal antibodies, and tyrosine kinase inhibitors [13, 14]

According to recent statistics, the most common cancers in prepubertal girls (age 0–14) are leukemia (31%), central nervous system malignancies (21%), lymphoma (10%), neuroblastoma (7%), Wilms tumor (5%), bone tumors (4%), rhabdomyosarcoma (3%) and retinoblastoma (3%). The most common cancers in female adolescents (age 15–19) are lymphoma (23%), leukemia (12%), thyroid (11%), central nervous system malignancies (10%), bone tumors (7%), melanoma (6%) and ovarian germ cell tumors (2%). The most common cancers in young women (age < 40) are breast (29%), lung (13%), colorectal (8%), uterine and cervical (6%) cancer, thyroid carcinoma (6%), lymphoma (4%), melanoma (4%), leukemia (3%), kidney (3%) and pancreatic (3%) cancer [9, 10].

However, the most common cancers during the female reproductive years that may require aggressive gonadotoxic chemotherapy and radiotherapy are breast, cervix, leukemia, lymphoma, central nervous system, renal and bone cancers [4–14]

2.2. Guidelines for preserving fertility of young women and girls with cancer

Due to recent advances in cancer diagnosis and treatment, the overall five-year survival rate in most cases of young women (age < 40) and girls with cancer has significantly increased up to ~90% [9, 10]. Accordingly, the topic how to prevent chemotherapy- and radiotherapy-induced gonadotoxicity and subsequent fertility loss has gained a growing attention.

Throughout the past 10 years, numerous international guidelines were published concerning anticancer treatments and female fertility. Such important guidelines were published by American Society of Clinical Oncology (ASCO) [13, 14], American Society for Reproductive Medicine (ASRM) [15, 16], European Society for Medical Oncology (ESMO) [17, 18], American Oncofertility Consortium (OC) [19, 20], International Society for Fertility Preservation (ISFP) [21, 22, 23, 24], Fertility Preservation Network FertiPROTEKT [25], American Academy of Pediatrics (AAP) [26], and Association of Pediatric Hematology/Oncology Nurses (APHON) [27].

In order to preserve fertility of young women (age < 40) and girls with cancer, several established, experimental, and debatable options can be offered in the emerging field of oncofertility. Established options include embryo or egg cryopreservation. Experimental options include ovarian tissue cryopreservation and further autotransplantation and/or in vitro maturation (IVM), while debatable options include surgical ovarian transposition (oophoropexy), gonadotropin-releasing hormone (GnRH) analogs and pelvic shielding [13–27].

3. Conclusion

We highlight that iatrogenic fertility loss in women is a serious complication of some anticancer treatments. Clinically, gonadotoxic agents such as aggressive chemotherapy and radiotherapy for treatment of cancer are the most common causes of pathological and iatrogenic fertility loss in women. In order to preserve fertility of young women (age < 40)

and girls with cancer, several established, experimental, and debatable options can be offered in the emerging field of oncofertility. Early referral by oncologists before initiation of chemotherapy and radiotherapy is an important key factor for success in female fertility preservation strategies.

4. Expert Commentary

4.1. Clinical concerns in preserving fertility of young women and girls with cancer

According to the most recent guidelines, all fertility preservation options mentioned above except in vitro maturation of ovarian tissue and follicles are currently used in clinical practice and have resulted in healthy live births [13–27]. Recently, the following success rates of female fertility preservation options have been reported: embryo cryopreservation (live birth rate of ~ 30% per frozen embryo transfer), egg cryopreservation (live birth rate of > 6% per frozen oocyte), ovarian tissue cryopreservation and further autotransplantation (live birth rate of ~25% per transplant) [25], oocyte in vitro maturation (live birth rate half of that for traditional IVF), and ovarian protection techniques (success rates are debatable) [13–27].

In spite of promising success rates, each fertility preservation option has both advantages and disadvantages and may not be suitable for all patients. Furthermore due to wide variations in the dose and dosage of anticancer treatments as well as the age and health conditions of cancer patients, success rates of female fertility preservation options in each case should be extrapolated with caution. It is also important to emphasize that patient's age plays a crucial role in estimating the success rate of any female infertility or oncofertility treatments. These concerns can be addressed by early counseling before initiation of chemotherapy and radiotherapy in order to tailor the most suitable fertility preservation strategy for each patient.

To provide fertility preservation services to young women (age < 40) and girls with cancer, the treating center should be properly equipped, and should have a highly skilled oncofertility team of oncologists, gynecologists, reproductive biologists, transplantation surgeons, and research scientists. Therefore, referring patients from oncology clinics, small medical centers or general hospitals to highly specialized oncofertility centers is strongly encouraged in order to guarantee a high standard of care [28, 29, 30].

We recommend that immediately after diagnosis of cancer, oncofertility counseling has to start. If the patient is below 40 and has a reasonable chance of survival, good health conditions and satisfactory reproductive functions, the plan of chemotherapy and radiotherapy should be checked and the risk of gonadotoxicity and subsequent fertility loss should be assessed. If the risk of gonadotoxicity and subsequent fertility loss is greater than 50% and the patient is willing to conceive in the future, a fertility preservation strategy should be performed before initiation of chemotherapy and radiotherapy.

From a clinical perspective, we suggest that the following three major strategies of female fertility preservation should be attempted respectively when not contraindicated: (i) Strategy one: Emergency or conventional hormonal ovarian stimulation followed by ovum pickup,

egg cryopreservation, and/or in vitro fertilization (IVF) and embryo cryopreservation (established options), (ii) Strategy two: Partial or unilateral oophorectomy followed by ovarian tissue cryopreservation and further autotransplantation and/or in vitro maturation (experimental options), (iii) Strategy three: Ovarian protection techniques such as oophropexy, pelvic shielding, GnRH analogs, and/or fractionated doses of chemotherapy and radiotherapy (debatable options). In strategy one, conventional hormonal ovarian stimulation is contraindicated in prepubertal girls and in women with estrogen sensitive tumors such as breast and endometrial cancers. In strategy two, ovarian autotransplantation is contraindicated in ovarian carcinomas and malignancies that may metastasize to ovaries such as leukemia, lymphomas, breast and gastrointestinal cancers. In strategy three, oophropexy and pelvic shielding do not provide ovarian protection when chemotherapy is used, while GnRH analogs do not provide ovarian protection when radiotherapy is used [31, 32, 33, 34]. In order to avoid such different contraindications, new advances in research to restore fertility of female cancer patients have been recently attempted including artificial ovary [35, 36, 37, 38], and use of mesenchymal stem cells [39, 40, 41].

When a patient cannot benefit from fertility preservation options, adoption or third party reproduction including egg donation, sperm donation, embryo donation and surrogacy may be considered as an alternative.

4.2. Barriers to oncofertility practice

In fact, there are several medical, economic, social and legal barriers that face oncofertility practice around the globe. Medical barriers may include lack of awareness among oncologists and gynecologists, lack of advances in early diagnosis and treatment of cancer, lack of referrals from oncologists, lack of inter-institutional communications, and lack of oncofertility specialists. Economic barriers may include lack of adequate health insurance coverage for fertility services, lack of institution and research fund, and the fact that most of fertility services are provided in private centers and paid as out-of-pocket services. All of these factors create a financial burden to the patients. Social barriers may include conservative cultural and religious attitudes towards third party reproduction, surrogacy and adoption. Legal barriers may include prohibition of third party reproduction, surrogacy and adoption due to cultural or religious reasons.

In Germany and USA, we experience common barriers while delivering fertility preservation services to young women and girls with cancer. Such common barriers are lack of awareness among physicians and inadequate health insurance coverage that may create financial burden to the patients. Unfortunately due to lack of awareness among oncologists and gynecologists, many young women and girls with cancer are not informed about preserving their fertility prior to chemotherapy and radiotherapy [42, 43, 44, 45]. As a result, many patients lose their fertility and become sterile. These patients will have no other options left to get children except considering adoption or third party reproduction including egg donation, sperm donation, embryo donation and surrogacy. As fertility services have become more internationalized, some patients prefer to travel abroad and get third party reproduction as a cross border reproductive care (CBRC) in order to protect their privacy or even to

circumvent law when third party reproduction is not legally allowed in their home countries [46, 47, 48, 49, 50, 51].

5. Five-year view

5.1. Overcoming barriers to oncofertility practice

To overcome the different barriers that arise in oncofertility practice especially in underserved areas, more effective solutions should be provided [52, 53, 54, 55]. For example, better awareness among oncologists, gynecologists and patients can be achieved via media, networks and sponsored scientific conferences and workshops. In Germany and USA particularly in the field of fertility preservation and oncofertility, two effective networks exist; FertiPROTEKT 56 and Oncofertility Consortium 57. FertiPROTEKT Network connects fertility preservation centers in all German-speaking countries (Germany, Austria and Switzerland), while Oncofertility Consortium Network located at Northwestern University, Chicago, USA connects fertility preservation centers in USA and worldwide as well. Such networks are the place where new ideas for oncofertility research projects develop, efforts of clinical care converge, and the interdisciplinary community of oncologists, gynecologists, reproductive endocrinologists, research scientists and patients participate in this cutting edge field.

As the field of fertility preservation expands, more attention towards the topic in the study programs of medical schools should be given in order to spread knowledge among medical students who will soon become future physicians. In addition, financial support for patients, technology, training and research can be achieved via grants and fundraising campaigns.

5.2. Enhancing oncologists' role in oncofertility practice

Undoubtedly, we consider oncologists as the most important players in oncofertility practice as they see cancer patients first and therefore they can initiate the process and inform patients about the available fertility preservation options and their advantages, limitations and success rates 58. Oncologists are also encouraged to communicate with gynecologists and refer their patients as early as possible for oncofertility counselling before initiation of chemotherapy and radiotherapy in order to tailor the most suitable fertility preservation strategy for each patient. In order to fill gaps in oncofertility practice and enable oncologists and gynecologists to communicate and take action, Oncofertility Consortium designed a specialized decision tools platform online 59. Such decision tools web portal provides information to help oncologists and gynecologists guide patients through their fertility preservation options and help them make the best decision based on their cancer treatment, lifestyle, values, and future fertility goals. The decision tools web portal also answers questions that are frequently asked by oncologists and gynecologists and related to the interest of cancer patients in oncofertility services, time needed to apply fertility preservation options before initiation of anticancer treatments, effect of fertility medications on cancer prognosis, costs and insurance coverage as well as issues related to contraception, hormonal replacement therapy, sex and sexuality during the course of cancer treatment 59.

6. Key issues

- Anticancer treatments such as aggressive chemotherapy and radiotherapy have deleterious gonadotoxic side effects.
- Anticancer treatments are considered the most common causes of pathological and iatrogenic fertility loss in women.
- In order to preserve fertility of young women (age < 40) and girls with cancer, several established, experimental, and debatable options can be offered in the emerging field of oncofertility.
- There are several medical, economic, social and legal barriers that face oncofertility practice around the globe.
- To overcome such barriers that arise in oncofertility practice especially in underserved areas, more effective solutions should be provided to spread awareness and enhance communication between patients, oncologists and gynecologists.
- Early referral by oncologists before initiation of chemotherapy and radiotherapy is an important key factor for success in female fertility preservation strategies.

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Abbreviations

AAP	American Academy of Pediatrics
ABVD	Doxorubicin (Adriamycin), Bleomycin, Vinblastine, Dacarbazine
AC	Doxorubicin (Adriamycin), Cyclophosphamide
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
APHON	Association of Pediatric Hematology/Oncology Nurses
ASCO	American Society of Clinical Oncology
ASRM	American Society for Reproductive Medicine
CAF	Cyclophosphamide, Doxorubicin (Adriamycin), Fluorouracil
CBRC	Cross Border Reproductive Care

CEF	Cyclophosphamide, Epirubicin, Fluorouracil
CMF	Cyclophosphamide, Methotrexate, Fluorouracil
CVP	Cyclophosphamide, Vincristine, Prednisone
EMSO	European Society for Medical Oncology
FertiPROTEKT	Fertility Preservation Network
GnRH	Gonadotropin-Releasing Hormone
HSCT	Hematopoietic Stem Cell Transplantation
ISFP	International Society for Fertility Preservation
IVF	In Vitro Fertilization
IVM	In Vitro Maturation
OC	Oncofertility Consortium
POF	Premature Ovarian Failure
TBI	Total Body Irradiation

References

Papers of special note have been highlighted as:

* of interest

** of considerable interest

1. De Vos M, Smitz J, Woodruff TK. Fertility preservation in women with cancer. Lancet. 2014;4;384(9950):1302–1310. [PubMed: 25283571] ** This report published in 2014 at Lancet reviewed the new advances to preserve fertility in women with cancer.
2. Jeruss JS, Woodruff TK. Preservation of fertility in patients with cancer. N Engl J Med. 2009;360(9):902–911. [PubMed: 19246362]
3. Salama M, Winkler K, Murach KF et al., Female fertility loss and preservation: threats and opportunities. Ann Oncol. 2013;24(3):598–608. [PubMed: 23129121]
4. Meirow D, Nugent D. The effects of radiotherapy and chemotherapy on female reproduction. Hum Reprod Update. 2001;7(6):534–543.
5. Green DM, Sklar CA, Boice JD, Jr, et al. Ovarian failure and reproductive outcomes after childhood cancer treatment: results from the Childhood Cancer Survivor Study. J Clin Oncol. 2009;27(14): 2374–2381. [PubMed: 19364956]
6. Anderson RA, Mitchell RT, Kelsey TW, Spears N, Telfer EE, Wallace WH. Cancer treatment and gonadal function: experimental and established strategies for fertility preservation in children and young adults. Lancet Diabetes Endocrinol. 2015; 3(7):556–567. [PubMed: 25873571]
7. Rodriguez-Wallberg KA, Oktay K. Fertility preservation during cancer treatment: clinical guidelines. Cancer Manag Res. 2014;6:105–117. [PubMed: 24623991]
8. Ferlay J, Soerjomataram I, Dikshit R,et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2014;136:E359–E386. [PubMed: 25220842]
9. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66(1):7–30. [PubMed: 26742998]

10. Ward E, DeSantis C, Robbins et al. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin 2014;64(2):83–103. [PubMed: 24488779]
11. Stroud JS, Mutch D, Rader J et al., Effects of cancer treatment on ovarian function. Fertil Steril. 2009;92(2):417–427. [PubMed: 18774559]
12. Meirow D, Biederman H, Anderson RA, Wallace W.Toxicity of chemotherapy and radiation on female reproduction. Clin Obstet Gynecol. 2010;53:727–739. [PubMed: 21048440]
13. Lee SJ, Schover LR, Partridge AH et al. American Society of Clinical Oncology. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol. 2006;24(18):2917–2931. [PubMed: 16651642]
14. Loren AW, Mangu PB, Beck LN et al. American Society of Clinical Oncology. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013;1;31(19):2500–2510. [PubMed: 23715580] ** This report published in 2013 by the American Society of Clinical Oncology (ASCO) classified anticancer treatments according to their risk of gonadotoxicity in women.
15. Ethics Committee of American Society for Reproductive Medicine. Fertility preservation and reproduction in patients facing gonadotoxic therapies: a committee opinion. Fertil Steril. 2013;100(5):1224–1231. [PubMed: 24094423]
16. Practice Committee of American Society for Reproductive Medicine. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril. 2013;100(5):1214–1223. [PubMed: 24011612] ** This report published in 2013 by the American Society for Reproductive Medicine (ASRM) offered guidelines for preserving fertility of patients who undergo gonadotoxic medical therapy or radiation therapy or gonadectomy.
17. Pentheroudakis G, Orecchia R, Hoekstra HJ, Pavlidis N; ESMO Guidelines Working Group. Cancer, fertility and pregnancy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21 Suppl 5:v266–v273. [PubMed: 20555095]
18. Peccatori FA, Azim HA, Jr, Orecchia R, et al. ESMO Guidelines Working Group.Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi160–vi170. [PubMed: 23813932]
19. Woodruff TK. The Oncofertility Consortium--addressing fertility in young people with cancer. Nat Rev Clin Oncol. 2010;7(8):466–475. [PubMed: 20498666]
20. Waimey KE, Duncan FE, Su HI, et al. Future Directions in Oncofertility and Fertility Preservation: A Report from the 2011 Oncofertility Consortium Conference. J Adolesc Young Adult Oncol. 2013;2(1):25–30. [PubMed: 23610740]
21. ISFP Practice Committee Kim SS, Donnez J, Barri P et al. Recommendations for fertility preservation in patients with lymphoma, leukemia, and breast cancer. J Assist Reprod Genet. 2012;29(6):465–468. [PubMed: 22648282]
22. Klemp JR, SS Kim ISFP Practice Committee. Fertility preservation in young women with breast cancer. J Assist Reprod Genet. 2012;29(6):469–472. [PubMed: 22614158]
23. Jadoul P, Kim SS; ISFP Practice Committee. Fertility considerations in young women with hematological malignancies. J Assist Reprod Genet. 2012;29(6):479–487. [PubMed: 22614159]
24. Schmidt KT, Andersen CY; ISFP Practice Committee. Recommendations for fertility preservation in patients with lymphomas. J Assist Reprod Genet. 2012;29(6):473–477. [PubMed: 22562284]
25. Van der Ven H, Liebenthron J, Beckmann M et al. FertiPROTEKT network. Ninety-five orthotopic transplantations in 74 women of ovarian tissue after cytotoxictreatment in a fertility preservation network: tissue activity, pregnancy and delivery rates. Hum Reprod. 2016;31(9):2031–2041. [PubMed: 27378768] ** This is the largest case series to date worldwide about cryopreservation and transplantation of ovarian tissue as a successful option for preserving fertility.
26. Fallat ME,Hutter J; American Academy of Pediatrics Committee on Bioethics; American Academy of Pediatrics Section on Hematology/Oncology; American Academy of Pediatrics Section on Surgery. Preservation of fertility in pediatric and adolescent patients with cancer. Pediatrics. 2008;121(5):e1461–e1469. [PubMed: 18450888]
27. Fernbach A, Lockart B, Armus CL et al. Evidence-Based Recommendations for Fertility Preservation Options for Inclusion inTreatment Protocols for Pediatr ic and Adolescent Patients Diagnosed With Cancer. J Pediatr Oncol Nurs. 2014;31(4):211–222. [PubMed: 24799444]

28. Woodruff TK. The emergence of a new interdiscipline: oncofertility. Cancer Treat Res. 2007;138:3–11. [PubMed: 18080653]
29. Woodruff TK. Oncofertility: a grand collaboration between reproductive medicine and oncology. Reproduction. 2015;150(3):S1–10. [PubMed: 26130814]
30. Ataman LM, Rodrigues JK, Marinho RM et al. Creating a Global Community of Practice for Oncofertility. J Glob Oncol. 2016;2(2):83–96. [PubMed: 27284576]
31. Gardino SL, Jeruss JS, Woodruff TK. Using decision trees to enhance interdisciplinary team work: the case of oncofertility. J Assist Reprod Genet. 2010;27(5):227–231. [PubMed: 20386978]
32. Salama M, Woodruff TK. New advances in ovarian autotransplantation to restore fertility in cancer patients. Cancer Metastasis Rev. 2015;34(4):807–822. [PubMed: 26589603] ** This report published in 2015 by the authors reviewed the updates in ovarian autotransplantation to restore fertility in cancer patients.
33. Salama M, Mallmann P. Emergency Fertility Preservation for Female Patients with Cancer: Clinical Perspectives. Anticancer Res. 2015;35(6):3117–3127. [PubMed: 26026071]
34. Salama M, Isachenko V, Isachenko E, et al. Updates in preserving reproductive potential of prepubertal girls with cancer: Systematic review. Crit Rev Oncol Hematol. 2016;103:10–21. [PubMed: 27184425]
35. Shea LD, Woodruff TK, Shikanov A. Bioengineering the ovarian follicle microenvironment. Annu Rev Biomed Eng. 2014;16:29–52. [PubMed: 24849592]
36. Luyckx V, Dolmans MM, Vanacker J, et al. First step in developing a 3D biodegradable fibrin scaffold for an artificial ovary. J Ovarian Res. 2013;6(1):83. [PubMed: 24274108]
37. Luyckx V, Dolmans MM, Vanacker J, et al. A new step toward the artificial ovary: survival and proliferation of isolated murine follicles after autologous transplantation in a fibrin scaffold. Fertil Steril. 2014;101(4):1149–1156. [PubMed: 24462059]
38. Soares M, Sahrari K, Chiti MC, et al. The best source of isolated stromal cells for the artificial ovary: medulla or cortex, cryopreserved or fresh? Hum Reprod. 2015;30(7):1589–1598. [PubMed: 25994668]
39. Xia X, Yin T, Yan J, et al. Mesenchymal Stem Cells Enhance Angiogenesis and Follicle Survival in Human Cryopreserved Ovarian Cortex Transplantation. Cell Transplant. 2015;24(10):1999–2010. [PubMed: 25353724]
40. Lai D, Wang F, Yao X, et al. Human endometrial mesenchymal stem cells restore ovarian function through improving the renewal of germline stem cells in a mouse model of premature ovarian failure. J Transl Med. 2015;13:155. [PubMed: 25964118]
41. Lai D, Wang F, Dong Z, Zhang Q. Skin-derived mesenchymal stem cells help restore function to ovaries in a premature ovarian failure mouse model. PLoS One. 2014;9(5):e98749. [PubMed: 24879098]
42. Gardino SL, Emanuel LL. Choosing life when facing death: understanding fertility preservation decision-making for cancer patients. Cancer Treat Res. 2010;156:447–458. [PubMed: 20811854]
43. Jungheim ES, Carson KR, Brown D. Counseling and consenting women with cancer on their oncofertility options: a clinical perspective. Cancer Treat Res. 2010;156:403–412. [PubMed: 20811851]
44. Redig AJ, Brannigan R, Stryker SJ, et al. Incorporating fertility preservation into the care of young oncology patients. Cancer. 2011;117(1):4–10. [PubMed: 21235031]
45. Köhler TS, Kondapalli LA, Shah A, et al. Results from the survey for preservation of adolescent reproduction (SPARE) study: gender disparity in delivery of fertility preservation message to adolescents with cancer. J Assist Reprod Genet. 2011;28(3):269–277. [PubMed: 21110080]
46. Cross-border reproductive care: an Ethics Committee opinion. Ethics Committee of American Society for Reproductive Medicine. Fertil Steril. 2016 pii: S0015–0282(16)62746–2.
47. Inhorn MC, Patrizio P. The global landscape of cross-border reproductive care: twenty key findings for the new millennium. Curr Opin Obstet Gynecol. 2012;24(3):158–163. [PubMed: 22366965]
48. Gürtin ZB, Inhorn MC. Introduction: travelling for conception and the global assisted reproduction market. Reprod. Biomed. Online 2011; 23(5):535–537. [PubMed: 21962528]
49. Collins J, Cook J. Cross-border reproductive care: now and into the future. Fertil. Steril 2010;94(1):e25–e26. [PubMed: 20149915]

50. Pennings G, de Wert G, Shenfield F et al. ESHRE task force on ethics and law 15: cross-border reproductive care. Hum. Reprod 2008;23(10):2182–2184. [PubMed: 18611918]
51. Salama M Cross Border Reproductive Care (CBRC): A Global Perspective. Obstet Gynecol Int J. 2014;1(2):00008.
52. Besharati M, Woodruff T, Victorson D. Young Adults' Access to Fertility Preservation Services at National Cancer Institute Community Oncology Research Program Minority/Underserved Community Sites: A Qualitative Study. J Adolesc Young Adult Oncol. 2016;5(2):187–200. [PubMed: 26812462]
53. Quinn GP, Woodruff TK, Knapp CA, et al. Expanding the Oncofertility Workforce: Training Allied Health Professionals to Improve Health Outcomes for Adolescents and Young Adults. J Adolesc Young Adult Oncol. 2016;5(3):292–296. [PubMed: 26978683]
54. Duncan FE, Jozefik JK, Kim AM, et al. The Gynecologist Has a Unique Role in Providing Oncofertility Care to Young Cancer Patients. US Obstet Gynecol. 2011;6(1):24–34. [PubMed: 21927621]
55. Woodruff TK. From the bench to bedside to babies: translational medicine made possible by funding multidisciplinary team science. J Assist Reprod Genet. 2013;30(10):1249–1253. [PubMed: 23975192]
56. Network FertiPROTEKT [Internet]. [cited 2017January 5]. Available from: <www.fertiprotekt.com>. ** FertiPROTEKT Network connects fertility preservation centers in all German-speaking countries including Germany, Austria and Switzerland.
57. Oncofertility Consortium Network [Internet]. [cited 2017January 5]. Available from: <www.oncofertility.northwestern.edu>. ** Oncofertility Consortium Network located at Northwestern University, Chicago, USA connects fertility preservation centers on both national and global levels.
58. Woodruff TK, Smith K, Gradishar W. Oncologists' Role in Patient Fertility Care: A Call to Action. JAMA Oncol. 2016;2(2):171–172. [PubMed: 26822528]
59. Decision tools web portal [Internet]. [cited 2017January 5]. Available from: <www.oncofertility.northwestern.edu/resources/oncofertility-decision-tool-web-portal>. ** The decision tools web portal of Oncofertility Consortium provides practical information to help oncologists and gynecologists guide patients through their fertility preservation options.

Table 1:

Risk of female gonadotoxicity with modern anticancer treatments adapted from the American Society of Clinical Oncology (ASCO) guidelines on fertility preservation in female patients with cancer [13].

Modern anticancer treatments for female patients	Risk of female gonadotoxicity
■ Hematopoietic stem cell transplantation (HSCT) with cyclophosphamide/total body irradiation (TBI) or cyclophosphamide/busulfan. ■ External beam radiation to a field that includes the ovaries. ■ CMF, CEF, CAF X 6 cycles in women age 40 and older (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, epirubicin).	**High risk (> 80%)**
■ CMF, CEF, CAF X 6 cycles in women age 30–39 (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, epirubicin). ■ AC X 4 cycles in women age 40 and older (adjuvant breast cancer therapy with doxorubicin/cyclophosphamide).	**Intermediate risk (20–80%)**
■ ABVD (doxorubicin/bleomycin/vinblastine/dacarbazine). ■ CHOP X 4–6 cycles (cyclophosphamide/doxorubicin/vincristine/prednisone). ■ CVP (cyclophosphamide/vincristine/prednisone). ■ Acute myeloid leukemia (AML) therapy (anthracycline/cytarabine). ■ Acute lymphoblastic leukemia (ALL) therapy (multi-agent). ■ CMF, CEF, CAF X 6 cycles in women less than 30 (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, epirubicin). ■ AC X 4 cycles in women less than 40 (adjuvant breast cancer therapy with doxorubicin/cyclophosphamide).	**Lower risk (< 20%)**
■ Methotrexate, fluorouracil, vincristine, bleomycin, dactinomycin.	**Very low or no risk**
■ Taxanes, oxaliplatin, irinotecan, monoclonal antibodies, tyrosine kinase inhibitors.	**Unknown risk (examples)**